REMARKS

Claims 1-38, 40, 50, 60, and 80-82 are pending and under consideration in the application. Claims 83-86 have been added. No new matter has been added. Claims 1, 2-4, 23, 38, 50, 55 and 60 have been amended herein.

The amendments to claims 1, 23, and 38, clarify that the cell includes one or more nucleic acids that together encode the destabilization domain, reporter moiety or target protein, and linker moiety. The use of nucleic acids to encode the destabilization domain, reporter moiety or target protein, and linker moiety is supported, for example, by page 38, line 6 to page 40, line 13, and Examples 8 and 9, which indicate that cells that include the destabilization domain, reporter moiety or target protein, and linker moiety can be obtained by introducing into the cell, one or more nucleic acids that encode the destabilization domain, reporter moiety or target protein, and linker moiety. Furthermore, the possibility that more than one nucleic acid molecule can be used that together encode the destabilization domain, reporter moiety or target protein, and linker moiety, is supported, for example, by page 44, lines 13-21, which clarify that two expression vectors can be used to express a reporter moiety, linker, and destabilization domain. The possibility that more than one nucleic acid molecule can be used is also supported for example, by page 36 lines 3-14, which clarify that a linker, for example, can include more than one separate polypeptide chain.

The amendment to claim 38 clarifying that the method includes a step wherein the target protein is recognized by one or more elements of a cellular protein degradation apparatus, is supported for example at page 24, lines 11-13. The amendments to claims 2, 3, 4, 50, 55, and 60 correct typographical errors. Newly added claims 83-84 are supported for example by the Examples which illustrate that cells used in methods of the invention can be from organisms that are not transgenic organisms. In addition, upon a reading of the specification as a whole, it will be recognized that although certain embodiments of the invention are directed at transgenic organisms, see for example, Section VII starting on page 59, line 15, methods of the invention can be practiced using cells from any organism including an organism that is not a transgenic organism. Newly added claim 85 wherein the cell is from

a transgenic rodent, is supported by page 59, line 15 to page 62, line 11, and more particularly page 60, line 19. Newly added claim 86 wherein the cell is from a transgenic plant, is supported by page 63, line 1 to page 67, line 29. Applicants respectfully request entry of the Amendment and reconsideration of the pending claims in view of the remarks and amendments herein. Upon entry of the Amendment, claims 1-38, 40, 50, 60, and 80-86 will be pending.

Claim Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1 to 15, 17 to 28, 30 to 38, 40 and 60 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification as filed. Applicants respectfully traverse the rejection. The Office Action acknowledges that claims 80-82 directed at aspects of the invention wherein the method is performed *in vitro*, are not included in this rejection. Applicants also note that claims 16 and 29 directed at aspects wherein the cell is a yeast cell, are not included in the rejection. Furthermore, claims 50 and 55 directed at recombinant DNA molecules are not included in the rejection.

The important question regarding the enablement requirement of 35 U.S.C. § 112, first paragraph is whether the experimentation needed to practice the invention is undue or unreasonable. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.01. The Office Action alleges that although the specification discloses how the claimed methods can be used *in vitro*, the claims are drawn to methods that encompass transgenic non-human mammals and the state of the art for the production of transgenic animals at the time of filing was allegedly unpredictable. Therefore, the Office Action alleges that undue experimentation would be required to practice the methods of the invention in a transgenic organism. Furthermore, the Office Action asserts that the level and specificity of expression of a transgene as well as the phenotype of a transgenic animal are dependent on the specific transgene construct used and are species dependent. Therefore, the Examiner concludes that the phenotype of a theoretical transgenic animal was unpredictable at the time of filing. Finally, the Office Action also alleges that the lack of enablement of the specification for the rejected claims is supported by

the fact that the specification does not indicate that any transgenic animal expressing the polypeptide of the invention has been made.

The Applicants respectfully assert that a skilled artisan could develop transgenic organisms to carry out methods of the pending claims, using the disclosure of the present application as filed, and methods well known in the art. Techniques for developing transgenic organisms have been available for over 20 years. The specification discloses many of these techniques, including a disclosure of techniques used for both transgenic animals and plants (See page 59, line 15 to page 67, line 29). Therefore, transgenic organisms can be developed that express the polypeptides of the present invention using standard techniques.

A skilled artisan would expect that the techniques would work to produce transgenic organisms expressing chimeric polypeptides of the present invention because there is nothing about the polypeptides of the present invention, or nucleic acids that express them, that would be expected to make them unusually difficult to express in a transgenic organism. For example, the transgenic organism would not be a knock-out organism, wherein the phenotype of the knock-out might be lethal. Furthermore, since the methods of certain aspects of the present invention rely on proteases that are present in virtually all eukaryotic cells, for example proteases of the ubiquitin/proteosome pathway, it would be expected that methods of the present invention could be performed in transgenic organisms of virtually any eukaryotic species.

The fact that some routine experimentation would be needed to produce a transgenic organism using the disclosure of the present application, does not render the application non-enabling. In fact, complex experimentation is not necessarily undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); MPEP § 2164.01. Production of transgenic organisms from recombinant DNA molecules, although possibly complex, is routine experimentation that is typically engaged in the biotechnology arts.

The fact that the present specification enables the methods and host cells of the invention as they relate to transgenic organisms, is confirmed by published reports of the

successful development of transgenic organisms that share important similarities with polypeptides of the present invention with respect to the development of transgenic organisms. For example, Tsirigotis et al., "Analysis of Ubiquitination *In Vivo* Using a Transgenic Mouse Model," *Biotechniques*, 31:120 (2001) (EXHIBIT A), teach the successful production of transgenic mice expressing a transgenic construct that encodes a chimeric polypeptide that includes polyhistidine tagged ubiquitin coupled to green fluorescent protein. Furthermore, Tsirigotis et al. teach that fluorescence of the green fluorescent protein of the expressed transgene can be detected in transgenic mice (See e.g., Tsirigotis et al., Figure 4 and page 124, middle column first full paragraph). In fact, Tsirigotis et al. produced the transgenic mice by injecting male pronuclei (See Tsirigotis et al., page 121, right column, first full paragraph), a method disclosed in the present application (page 60, lines 27-29). Therefore, Tsirigotis et al. confirm that expression of chimeric reporter constructs that include a ubiquitin moiety coupled to a reporter can be successfully accomplished using standard techniques for producing transgenic organisms.

In addition to transgenic mice expressing chimeric ubiquitin constructs, transgenic plants expressing chimeric ubiquitin constructs have also been developed. For example, Bachmair et al. developed transgenic *Arabidopsis thaliana* lines that express a reporter moiety (i.e., dihydrofolate reductase (DHFR)) coupled to ubiquitin. *Proc. Natl. Acad. Sci.* USA, 90, 418 (1992) (EXHIBIT B). Furthermore, Bachair et al., demonstrate that DHFR activity in the transgenic *Arabidopsis* plants can be detected by assaying for MTX resistance. *Id.* Hondred et al. teach that chimeric ubiquitin protein fusions can be synthesized and accurately processed in tobacco. *Plant Physiology*, 119, 713 (1999) (EXHIBIT C). The chimeric polypeptides expressed by Hondred et al. include a ubiquitin moiety coupled to a number of reporter moieties and target proteins including glucuronidase, luciferase, amylase, and acyl carrier protein. Therefore, Bachmair et al., and Hondred et al. confirm that transgenic organisms that express chimeric polypeptides that include a ubiquitin moiety coupled to a reporter moiety can be successfully developed using standard techniques for producing transgenic plants. Accordingly, claims 1 to 15, 17 to 28, 30 to 38, 40 and 60 are enabled by the disclosure of the

present application as filed, and Applicants respectfully request withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph. It is noteworthy that newly added claims 83-84 are directed to methods in which the cell is from an organism other than a transgenic organism, and that newly added claim 85 is directed to a transgenic mouse and claim 86 to a transgenic plant.

Claim Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1 to 38, 40 and 80 to 82 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being incomplete for omitting essential elements, allegedly amounting to a gap between the elements. Applicants respectfully traverse the rejection.

The Office Action asserts that the claims must include an indication that the cells include a nucleic acid encoding the chimeric polypeptide. The Office Action alleges that without a clear indication that the cell includes the nucleic acid that encodes the polypeptide, it is allegedly unclear how the cell would include the chimeric polypeptide as no guidance or methods are known.

Claims 1, 23, and 38, from which the remaining claims included in this rejection depend, are amended herein to clarify that the cell includes one or more nucleic acids that together encode the destabilization domain, the reporter moiety or target protein, and the linker. Therefore, the rejection of claims 1 to 38, 40 and 80 to 82 under 35 U.S.C. § 112, second paragraph, has been overcome. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 1 to 22, 38, 40 and 60 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Regarding claims 1 to 22, the Office Action alleges that the claims are indefinite because there is no requirement or active or positive step in the claims that the activity is detected. Regarding claims 38 and 40, the Office Action alleges that the claims are indefinite because there is no requirement or active or positive step in the claims that the target protein is destabilized. Regarding claim 60, the Office Action alleges that the

phrase "a nucleic acid sequence encoding for" renders the claim indefinite because it is unclear how a nucleic acid "encodes for" anything. The Office Action recommends amending the claim to recite "a nucleic acid sequence encoding." Applicants respectfully traverse the rejection of claims 1 to 22, 38, 40 and 60.

Claim 1, from which claims 2 to 22 depend, has been amended herein to further clarify that by detecting the reporter moiety or a product of the reporter moiety, the method includes a step wherein the activity is detected. Claim 38 from which claim 40 depends, has been amended herein to clarify that the method involves a step wherein the target protein is recognized by one or more elements of a cellular protein degradation apparatus. Claim 60 has been amended herein as suggested by the Examiner, to clarify that the nucleic acid sequence encodes the destabilization domain, the target protein, and the linker moiety. Therefore, the rejection of claims 1 to 22, 38, 40 and 60 under 35 U.S.C. § 112 has been overcome, and Applicants respectfully request withdrawal of the rejection.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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